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Use of a New Spirophosphine to Achieve Catalytic Enantioselective [4+1] Annulations of Amines with Allenes to Generate Dihydropyrroles

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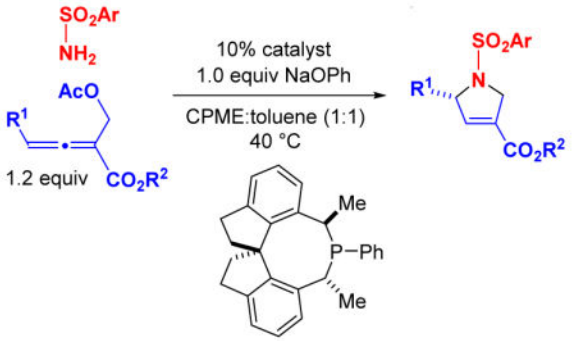
Abstract



Due in part to the common occurrence of five-membered nitrogen heterocycles in bioactive molecules, the discovery of methods for the enantioselective synthesis of such structures is a useful endeavor. Building on a single example by Tong of a phosphine-catalyzed [4+1] annulation of an amine with an allene that furnished an achiral dihydropyrrole in 22% yield, we have developed, with the aid of a new chiral spirophosphine catalyst, a method with increased utility, specifically, improved yield, enhanced scope (the use of γ-substituted allenes), and good ee. The enantioenriched dihydropyrrole products can be transformed into other interesting families of compounds with very good stereoselectivity.

Chiral five-membered nitrogen heterocycles, including pyrrolidines and 2,5-dihydropyrroles, are found in a wide array of bioactive compounds.[1–4] One powerful, convergent method for the synthesis of 2,5-dihydropyrroles is the phosphine-catalyzed [3+2] coupling of an imine with an allene, first reported by Lu in 1997;[5] not surprisingly, during the past several years, a great deal of effort has been directed at the development of an enantioselective variant of this annulation process, and substantial progress has been described (eq 1).[6,7]

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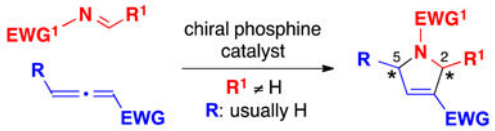
The authors declare no competing financial interest.

Supporting Information

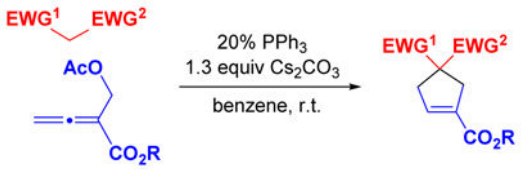
Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.



(1)

Although relatively broad in scope, the Lu [3+2] annulation does not provide access to the full spectrum of substituted 2,5-dihydropyrroles, for example those in which R^1 = H (eq 1). In 2010, Tong reported a novel PPh_3-catalyzed [4+1] annulation of 1,1-bisnucleophiles and allenes that furnishes racemic cyclopentenes (eq 2);[8] very recently, enantioselective variants of this useful process have been developed.[9] Tong also provided a single example of the use of a nitrogen nucleophile ($TsNH_2$) in such a [4+1] annulation, affording an achiral 2,5-dihydropyrrole in somewhat modest yield (22%; eq 3).

In recent years, we have been exploring the use of chiral DMAP derivatives and phosphines as nucleophilic catalysts for a diverse array of asymmetric processes.[10,11] In order to access a complementary set of enantioenriched 2,5-dihydropyrroles that cannot be generated by Lu's [3+2] annulation, we decided to pursue the development of the catalytic asymmetric [4+1] annulation illustrated in eq 4. In the proposed transformation, the newly formed stereocenter emanates from a prochiral carbon of the allene, in contrast to recently described enantioselective phosphine-catalyzed [4+1] Tong annulations of carbon bisnucleophiles, wherein the stereocenter is derived from a prochiral nucleophile (eq 2).[9]



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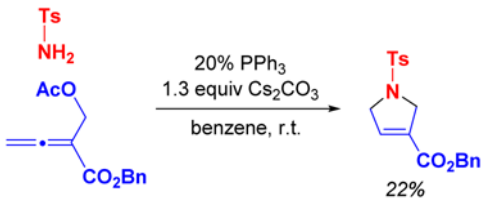

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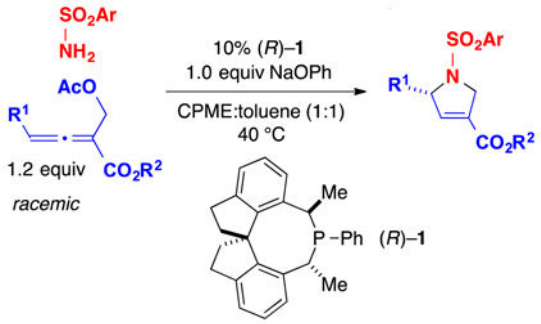


(4)

Relative to the state-of-the-art for this phosphine-catalyzed approach to generating 2,5-dihydropyrroles (eq 3), a number of key challenges needed to be addressed, including: improving the yield of the [4+1] annulation; developing a general method that can employ γ-substituted allenes; and, achieving high enantioselectivity. In this report, we describe the achievement of these objectives with the aid of a new chiral spirophosphine catalyst (**1**; eq 4).

Although a variety of phosphine-catalyzed annulation reactions of allenes have been developed, most investigations have focused on allenes that lack a γ substituent,[7] due in part to the propensity of many γ-substituted substrates to undergo phosphine-catalyzed isomerization to 1,3-dienes;[12] for example, to the best of our knowledge, there is only one example of a phosphine-catalyzed [4+1] annulation that utilizes a γ-substituted allene.[9b] Nevertheless, because our objective necessitated that we employ such an allene as a reaction partner, we focused our efforts on developing a method to achieve the [4+1] annulation illustrated in Table 1.

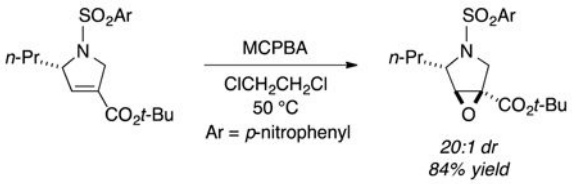
Under the conditions described in Table 1, spirophosphine **2**,[13] which we have established can serve as an effective chiral nucleophilic catalyst for an array of other processes,[14] furnishes the desired dihydropyrrole in excellent yield and moderate enantiose-lectivity (entry 1). We decided to synthesize a new spirophosphine catalyst (**1**),[15] and we were pleased to determine that it achieves the desired [4+1] annulation in very good yield and ee (93% yield, 92% ee; entry 2). In the absence of a catalyst, no dihydropyrrole is generated under these conditions (entry 3). Use of a lower catalyst loading leads to a significantly lower yield; however, this can be alleviated if the amount of allene is increased (1.2→1.5 equivalents; entries 4 and 5). If NaOPh is omitted, the annulation proceeds with diminished enantioselectivity (entry 6), and replacement of NaOPh with another base provides poorer results (Cs_2CO_3; entry 7). Similarly, conducting the [4+1] reaction at lower temperature (entry 8) or in only toluene or only CPME (entries 9 and 10) leads to somewhat reduced yield or ee. The process is not particularly air- or moisture-sensitive (entries 11 and 12).[16]

With effective annulation conditions in hand, we investigated the scope of this new method for the catalytic asymmetric synthesis of dihydropyrroles (Table 2). The identity of the ester substituent (R^2) has essentially no impact on yield and at most a small effect on

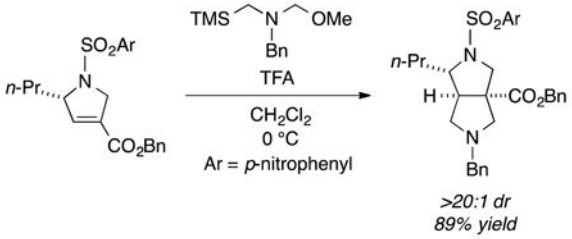
enantioselectivity (entries 1–3). The γ substituent of the allene can be β-branched (entries 4 and 5), although very little of the desired product is generated under these conditions when R^1 = isopropyl. The catalytic enantioselective [4+1] annulation proceeds smoothly in the presence of functional groups such as an alkyne, a silyl ether, a dialkyl ether, an imide, and a thiophene (entries 6–10). For reactions wherein relatively modest enantiose-lectivity is observed in the annulation, the ee can be enhanced through recrystallization (entry 4). On a gram-scale, the dihydropyrrole synthesis depicted in entry 7 proceeds in 87% yield and 90% ee.[17]

We have also examined the scope of this catalytic asymmetric [4+1] annulation with regard to the sulfonamide coupling partner (Table 3).[18] Replacing the nitro group with another electron-withdrawing group, such as cyano (entry 1) or trifluoromethyl (entry 2), has little effect on the outcome of the reaction, as does moving it to the ortho position (entry 3). However, somewhat lower yield and ee are observed if the aromatic group is not electron-poor (entry 4).

The dihydropyrrole products of these [4+1] annulations serve as useful precursors to other interesting and stereochemically rich compounds. For example, epoxidation and cycloaddition reactions proceed with high diastereoselectivity (eq 5 and eq 6).



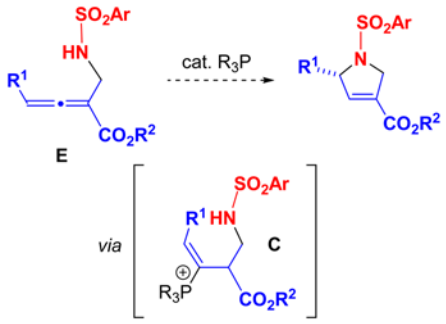
(5)



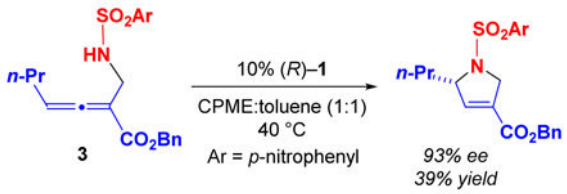
(6)

A possible mechanism for this phosphine-catalyzed synthesis of dihydropyrroles is depicted in Figure 1.[8] β-Addition of the nucleophilic phosphine to the allene and expulsion of the acetate generates diene **A**. Next, the sulfonamide can add to either olefin, furnishing **B** and/or **C**. Finally, intramolecular addition of the sulfonamide to the other olefin affords intermediate **D**, which then undergoes elimination to provide the dihydropyrrole and regenerate the phosphine catalyst.

During some of these annulation reactions, a small amount of adduct **E** is observed.[19] To gain insight into whether compound **E** (and therefore, potentially, intermediate **C** in Figure 1) is chemically competent (eq 7), allene **3** was treated with spirophosphine catalyst (*R*)-**1**; the dihydropyrrole was indeed formed, and with high ee (with the "expected" absolute stereochemistry; eq 8).

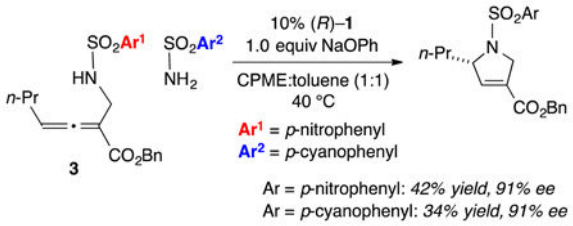


(7)



(8)

Next, a crossover experiment was performed, employing allene **3** and *p*-cyanobenzenesulfonamide (eq 9). The nitro- and the cyano-containing dihydropyrroles were produced in similar yields, consistent with the suggestion that the addition of the sulfonamide to the α,β-unsaturated ester in intermediate **A** (Figure 1) may be reversible under the reaction conditions.[20]



(9)

Finally, we have established through ^{31}P NMR spectroscopy that the primary resting state of catalyst **1** during the [4+1] annulation process is the free phosphine (~94%), accompanied by a small amount (~6%) of a second compound with a resonance at δ 44. In the ESI–MS spectrum of a reaction mixture, the major cationic species that is observed has *m/z* = 577, which corresponds to phosphonium salt **A** (Figure 1).[21]

In summary, we have developed the first effective nucleophile-catalyzed method for the [4+1] annulation of amines with allenes to generate dihydropyrroles, a useful family of nitrogen heterocycles. Specifically, with the aid of a new chiral spirophosphine catalyst, we have achieved the enantioselective coupling of sulfonamides with an array of allenes that are substituted in the γ position; such allenes have rarely served as suitable partners in phosphine-catalyzed [4+1] annulations. The olefin of the dihy-dropyrrole product is poised for stereoselective derivatization to furnish highly functionalized, stereochemically rich products. Further studies of enantioselective nucleophile-catalyzed reactions are underway.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This study is dedicated to Prof. Stephen L. Buchwald, a friend and a mentor, on the occasion of his 60th birthday. Support has been provided by the National Institutes of Health (National Institute of General Medical Sciences: R01–GM57034) and the Lundbeck Foundation (postdoctoral fellowship for S.K.). We thank Dr. Nathan D. Schley, Dr. Michael K. Takase (Caltech X-ray Crystallography Facility; a Bruker KAPPA APEX II X-ray diffractometer was purchased via NSF CRIF:MU award CHE-0639094 to Caltech), Dr. David G. VanderVelde (Caltech NMR Facility), Dr. Scott C. Virgil (Caltech Center for Catalysis and Chemical Synthesis, supported by the Gordon and Betty Moore Foundation), and Dr. Susan L. Zultanski (initial synthesis of phosphine **1**) for assistance.

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Kwon O. Science of Synthesis: Asymmetric Organocatalysis. List B, Maruoka K. Georg Thieme VerlagStuttgart2012; 1:723–782.

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15. After exposure to air as a solid in an open vial for 30 days, no decomposition or oxidation of phosphine **1** was detected by ^{31}P or ^{1}H NMR spectroscopy; after 5 months under these conditions, a small amount (~3%) of the phosphine oxide was observed. After exposure to air in solution (CPME:toluene 1:1, “sparged” with air) for 24 hours, ~20% of the phosphine oxide was observed.
16. Notes: (a) The ee of the dihydropyrrole was constant during the course of the reaction. (b) If a slight excess of the amine, rather than a slight excess of the allene, is used (1.2 equiv), the annulation proceeds in 85% yield and 92% ee.
17. The catalyst was recovered in 81% yield.
18. The p-nitrobenzenesulfonyl group can be removed through treatment with $PhSH/K_2CO_3$ in DMF at room temperature: Fukuyama T, Jow CK, Cheung M. Tetrahedron Lett. 1995; 36:6373–6374.
19. Under our standard annulation conditions: the formation of adduct **E** was not observed in the absence of phosphine **1**; adduct **E** comprised <10% of the reaction mixture during the course of the annulation. (b) For a related observation, see: Hu J, Tian B, Wu X, Tong X. Org Lett. 2012; 14:5074–5077. [PubMed: 22994290]
20. Under different conditions, related adducts (without a γ substituent) undergo cyclization to a dihydropyrrole in the presence of an achiral phosphine (PPh3): Andrews IP, Blank BR, Kwon O. Chem Commun. 2012; 48:5373–5375. The mechanism of this process was not examined. (b) Under the same conditions in the absence of phosphine, no dihydropyrrole was observed.
21. (a) The use of carboxylate leaving groups other than acetate led to essentially identical ee and to either slightly (benzoate and pivalate) or considerably (trichloroacetate) lower yield. (b) During the course of a [4+1] annulation, the ee of the unreacted allene was low (<10%). (c) If enantioenriched allene is subjected to the annulation conditions, essentially no racemization of the allene is observed at partial conversion. (d) Because of the heterogeneity of the reaction mixture, due to the relatively low solubility of the sulfonamides in CPME:toluene, we have not been able to perform meaningful kinetics and relative-reactivity studies.

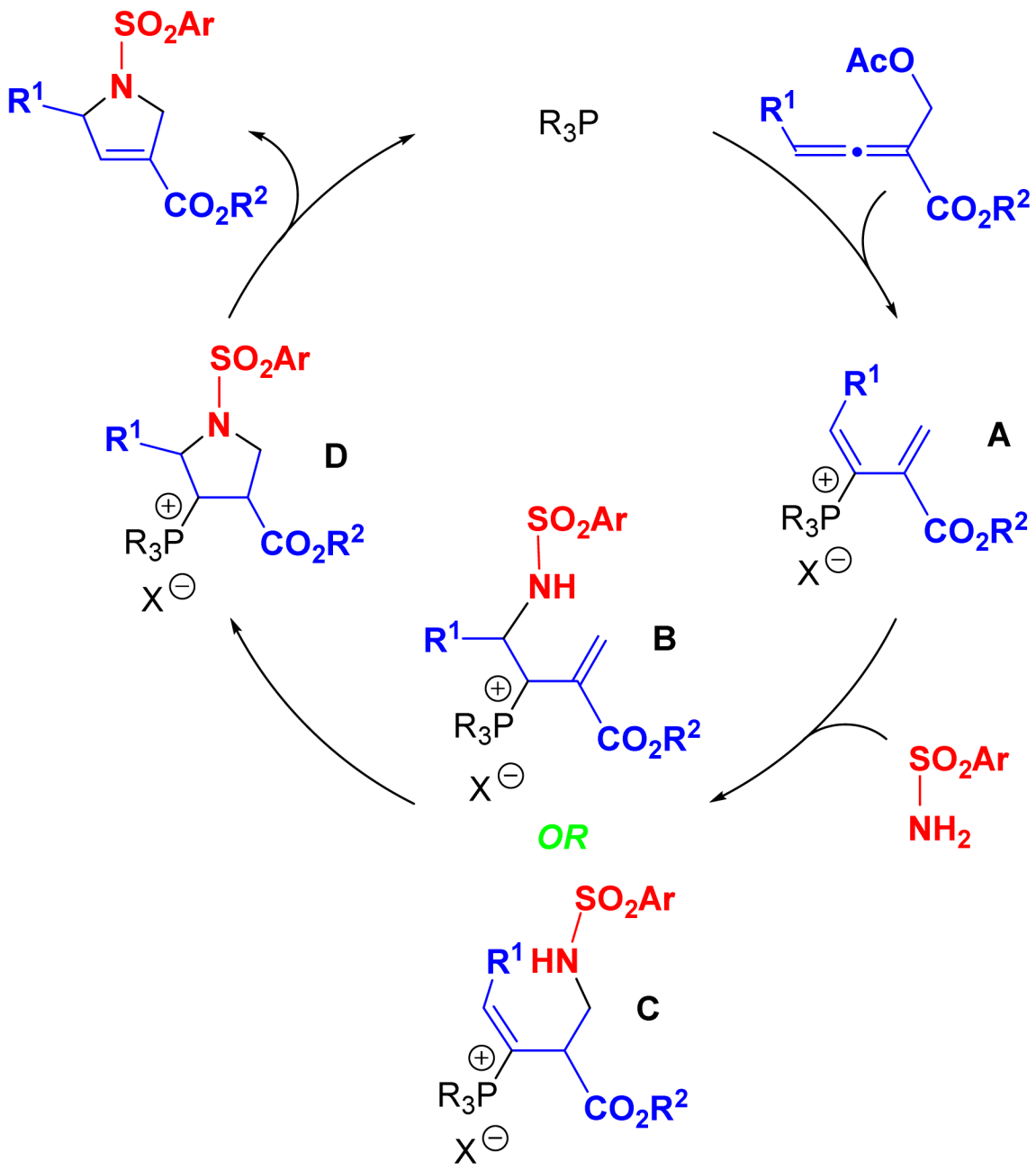
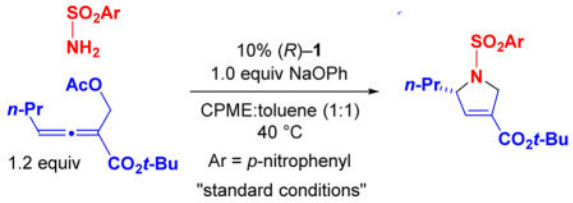


Figure 1.

Outline of a possible mechanism for phosphine-catalyzed [4+1] annulations to generate dihydropyrroles (for the sake of simplicity, all steps are drawn as irreversible, alkenes are illustrated as single isomers, and intermediates are illustrated as positively charged phosphonium salts).

Table 1

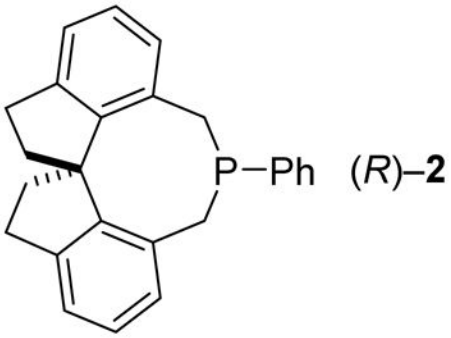
The Effect of Reaction Parameters on a Phosphine-Catalyzed Enantioselective [4+1] Annulation to Generate an Enantioenriched Dihydropyrrole[a]



entry	change from the "standard conditions"	yield (%)[b]	ee (%)
1	(*R*)-**2**, instead of (*R*)-**1**	97	63
2	none	93	92
3	no (*R*)-**1**	<1	–
4	5% (*R*)-**1**	68	92
5	5% (*R*)-**1** and 1.5 equiv allene	86	91
6	no NaOPh	97	78
7	Cs_2CO_3, instead of NaOPh	62	88
8	r.t.	81	92
9	toluene, instead of CPME and toluene	97	88
10	CPME, instead of CPME and toluene	80	91
11	under air (capped vial)	85	92
12	added H_2O (0.5 equiv)	90	91

[a] All data are the average of two or more experiments.

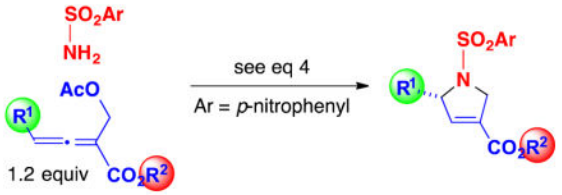
[b] Determined through the use of ^1H NMR spectroscopy, with Bn_2O as an internal standard.

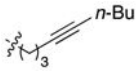
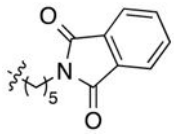
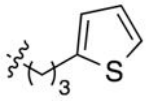


(*R*)–**2**

Table 2

Phosphine-Catalyzed [4+1] Annulations to Generate Enantioenriched Dihydropyrroles: Scope with Respect to the Allene[a]



entry	R1	R2	yield (%)[b]	ee (%)
1	*n*-Pr	Et	94	87
2	*n*-Pr	Bn	90	91
3	*n*-Pr	*t*-Bu	93	92
4	*i*-Bu	Bn	84	87[c]
5	*i*-Bu	*t*-Bu	78	93
6		*t*-Bu	90	90
7		*t*-Bu	90	91
8		*t*-Bu	92	91
9		*t*-Bu	92	91
10		*t*-Bu	95	89

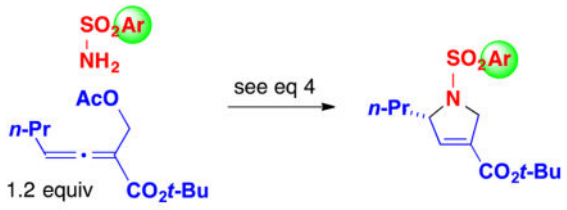
[a] All data are the average of two experiments.

[b] Yield of purified product.

[c] After one recrystallization: 62% yield and 99% ee.

Table 3

Phosphine-Catalyzed [4+1] Annulations to Generate Enantioenriched Dihydropyrroles: Scope with Respect to the Sulfonamide[a]



entry	Ar	yield (%)[b]	ee (%)
1	*p*-cyanophenyl	92	92
2	*p*-(trifluoromethyl)phenyl	88	90
3[c]	*o*-nitrophenyl	67	91
4	phenyl	74	83

[a] All data are the average of two experiments.

[b] Yield of purified product.

[c] Catalyst loading: 20%.